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1) A method of producing a therapeutic reagent comprising human cells that may be depleted in-vivo as part of an cell therapy treatment, said method comprising:

(a) Providing human cells;

(b) Ex-vivo inducing specific drug hypersensitivity into said human cell by selectively inhibiting the expression of at least one gene, said gene being directly or indirectly involved in the metabolization, elimination or detoxification of said specific drug,

(c) Optionally assaying the hypersensitivity of the human cell engineered in step b) to said drug;

(d) Culturing the engineered immune cells obtained in step b).

2) A method to claim **1**, wherein said human cells are human hematopoietic stem cells (hHSC), and preferably human primary cells.

3) A method to any one of claim **1** or **2**, wherein said human cells are immune cells, preferably T cells.

4) A method to any one of claims **1** to **3**, wherein said gene inhibition in step (b) is a long term inhibition, preferably by gene editing.

5) A method of claim **4**, wherein said gene editing is obtained by introducing into said human cell, preferably immune cell, at least one rare-cutting endonucleases or targeted nickase targeting said gene.

6) The method according to claim **5**, wherein said rare-cutting endonuclease is a TALE-nuclease or Cas9.

7) A method of any one of claims **1** to **6**, wherein said at least one gene which expression is inhibited or inactivated is selected from the group consisting of genes encoding for GGH, RhoA, CDK5, CXCR3, NR1H2, URG4, PARP14, AMPD3, CCDC38, NFU1, CACNG5 and SAMHD1 polypeptide.

8) A method of any one of claims **1** to **7**, wherein the expression of GGH is inhibited conferring hypersensitivity to 5-FU and resistance to methotrexate.

9) A method of claim **8**, wherein said rare-cutting endonuclease has as target the gene under the NCBI Reference Sequence NP_003869.1 encoding for human GGH enzyme.

10) A method of claim **8** or **9**, wherein said rare-cutting endonuclease targets a sequence of SEQ ID NO:14, or to a sequence having at least 95% identity with the SEQ ID NO:15.